

Rapid alteplase administration improves functional outcomes in stroke patients with large vessel

occlusions: Meta-analysis of the non-interventional arm from the HERMES collaboration

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ABSTRACT

Background and Purpose:

We report the relation of onset to treatment time (OTT) and door to needle time (DTN) with functional outcomes and mortality among ischemic stroke patients with imaging-proven large vessel occlusion (LVO) treated with intravenous alteplase.

Methods:

Individual patient-level data from the HERMES collaboration were pooled from seven trials that randomised patients to mechanical thrombectomy added to best medical therapy versus best medical therapy alone. Analysis was restricted to patients who received alteplase directly at the endovascular hospital. The primary outcome was disability defined on the modified Rankin Scale (mRS) at 3 months.

Results

Among 601 patients, mean age was 66.0 years (SD 13.9), 50% were women, and median NIHSS score was 17. Onset to treatment (OTT) time was median 125 minutes (IQR 90-170). Door-to-treatment time was median 38 minutes (IQR 26-55). Each 60-minute OTT delay was associated with greater disability at 90 days; the odds of functional independence (mRS 0-2) at 90 days was OR 0.82 (95%CI, 0.66 to 1.03). With each 60-minute delay in door-to-needle time, the odds of functional independence was OR 0.55 (95%CI, 0.37 to 0.81) at 90 days. The absolute decline in the rate of excellent outcome (mRS 0-1 at 90 days) was 20.3 per 1000 patients treated per 15 minutes delay in door-to-needle time. The adjusted absolute risk difference for a door-to-needle time < 30 min vs. 30-60 min was 19.3% for independent outcome (NNT ~ 5 to gain one additional good outcome). SICH occurred in 3.4% of patients, without a significant time dependency: OR 0.74 (95CI 0.43-1.28).

Conclusion

Faster intravenous thrombolysis delivery is associated with less disability at 3 months among patients with large vessel occlusion.

INTRODUCTION

Multiple randomised controlled trials (RCTs) have demonstrated the superiority of endovascular thrombectomy (EVT) in combination with intravenous alteplase over alteplase alone among patients with ischemic stroke due to large vessel occlusion (LVO).¹ Prior evidence shows a time-dependent benefit of alteplase among all fibrinolysis-eligible patients with acute ischaemic stroke within 4.5 hours.² However, alteplase alone yields lower early reperfusion rates in patients with large vessel occlusions, compared with medium and small vessel occlusions, and the degree and time-dependence of benefit of alteplase in LVO stroke patients is less well understood since RCTs comparing intravenous alteplase to control did not require pre-treatment neurovascular imaging.^{3,4} Better understanding of these aspects of alteplase treatment would be helpful in determining the risks and benefits of delaying alteplase start but hastening thrombectomy start by ambulance routing of patients directly to interventional stroke centers.

Additionally, the number of exclusion criteria for alteplase therapy, its cost, the time required for its mixing and infusion and safety considerations are cited reasons⁵ to justify trials randomizing LVO patients destined to undergo EVT to either receive alteplase therapy vs. placebo.⁶

Prior data on alteplase use in proven LVO cohorts are limited. Some studies relied on transcranial Doppler to diagnose the presence of intracranial occlusions, which is an operator-dependent technique and which also might confound observational studies by introducing a sonothrombolysis treatment effect.⁷ With the recent advent of large-scale endovascular thrombectomy trials and routine endovascular thrombectomy practice, there has been a shift in the standard stroke imaging paradigm with acute intracranial vessel imaging becoming a routine modality. In a meta-analysis, intravenous alteplase showed greater effect among patients with proven pre-treatment occlusion.⁸ Recent successful randomised controlled trials of EVT relied on CT or MR angiography to detect the occlusion location. Some of the trials used at least one extra imaging modality to assess collaterals or brain perfusion to select patients most likely to benefit from revascularization therapies.⁹⁻¹⁵ We pooled individual patient data from patients with LVO treated with intravenous alteplase alone in the controls arms of seven recent RCTs of

EVT, and explored the impact of interval times adjusting for important prognostic clinical and imaging variables on functional recovery and adverse outcome.

METHODS

The Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials (HERMES) collaboration was formed by the trial investigators of ESCAPE, EXTEND-IA, MR CLEAN, PISTE, REVASCAT, SWIFT PRIME and THRACE. We searched Pubmed for randomized trials published between 1 Jan 2010 and 31 May 2017 comparing endovascular thrombectomy performed using predominantly stent-retrievers with standard care in anterior circulation ischaemic stroke patients - Pubmed search string: (("randomized controlled trial"[Publication Type]) AND ((thrombectomy[Title/Abstract]) OR (clot retrieval[Title/Abstract]) OR intraarterial[Title/Abstract]) AND (stroke[Title/Abstract]) AND ("2010/01/01"[Date - Publication] : "2017/05/31"[Date - Publication])). The design and selection criteria of these trials and the HERMES collaboration have been previously described.¹ In brief, these trials randomised patients to receive EVT using retrievable stents (in most patients) plus medical therapy vs. medical therapy alone in anterior circulation ischaemic stroke patients. The current study included only medical therapy (control) arm patients who received intravenous alteplase. From this population, we excluded patients who received alteplase in a peripheral hospital prior to transfer to the endovascular center, since among these patients the RCTs selectively enrolled only alteplase-failure patients, Alteplase was administered according to clinical routine standard care with a total dose of 0.9 mg/kg with 10% of the dose given as a bolus and the remainder infused over an hour. All participants provided informed consent according to each trial protocol and each study was approved by the local ethics board.

This meta-analysis was prospectively designed by the HERMES executive committee but not registered. Data were contributed by the authors of all the trials meeting eligibility criteria and collated by independent statisticians. All data relevant to the analyses presented were part of each study's individual design and data collection and are part of the general HERMES database. No standardization or translation of the fields employed for analysis and reporting was necessary. After collation of data, key fields were compared to original results, including published data. No major discrepancies were found and minor discrepancies were resolved in collaboration with the study authors/investigators. The principal risk of bias derived from differences among individual studies' methods and inclusion criteria.

Outcomes

Global disability status at 90 days was assessed using the modified Rankin Scale (mRS). The primary outcome was the degree of disability at 90 days on the mRS, tested with the common odds ratio from a proportional odds model. Categories 5 and 6 were collapsed into one resulting in a 6-level scale.

Secondary efficacy outcomes were: excellent recovery (mRS 0-1) and independent recovery (mRS 0-2). Safety outcomes were death (mRS 6) and symptomatic intracranial haemorrhage (sICH) defined within each trial.

Statistical Analysis

We assessed outcomes using generalised linear mixed models, including a cumulative logit link function for the multinomial primary outcome of mRS and a logit link function for all other (binomial) outcomes. In all models, a term for study was included as a random effect to account for study-level variation. The relation between time and outcomes was adjusted for age, sex, baseline NIHSS score, ASPECT score and occlusion location. We also assessed for evidence of interaction between time and key baseline factors (age, sex, baseline NIHSS score, ASPECT score, occlusion location, diabetes mellitus, atrial fibrillation, and prior stroke). We calculated the rate of decline in benefit per 1000 patients treated by assuming linearity of the relationship and then calculating the slope of the line. All statistical analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 3.2 (R Foundation for

Statistical Computing, Vienna, Austria). P-values were two-sided and $p < 0.05$ indicated statistical significance in all analyses.

Role of the funding source

The funder of the study had no role in study design, data collection, analysis, or interpretation, writing of this article, or the decision to submit this study for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Among 893 patients in the control arms, 86 (9.6%) were excluded as being alteplase-ineligible and 206 (23.1%) as receiving alteplase at a non-endovascular center, leaving 601 (67.3%) receiving alteplase at the endovascular hospital. Among these 601 patients, mean age was 66.0 years (SD 13.9), 50% were women, and median NIHSS score was 17 (IQR 13-21). The median time from onset to intravenous alteplase start was 165 minutes (IQR 130-203), with 82% treated within 3 hours from onset and 17% between 3-4.5 hours. The median door-to-alteplase-treatment time was 38 minutes (IQR 26 – 55). Patient characteristics according to onset to treatment time in early (0-90 minutes), intermediate (91-180 minutes), and late (181-270 minutes) windows are shown in Table 1. Patients in each time treatment epoch were well-matched with respect to age and sex. Earlier-treated patients were less likely to have a history of hypertension and hyperlipidaemia, less severe infarct signs on imaging (higher ASPECT scores), higher acute serum glucose levels, more often had occlusions in the internal carotid artery (ICA) and presented with more severe deficits (higher NIHSS scores).

At 90 days, 20.2% (118/583) achieved excellent recovery (mRS 0-1) and 34.1% (199/583) achieved independent functional recovery (mRS 0-2). In adjusted analyses, the odds of better disability outcomes at 90 days (mRS scale distribution) in the alteplase group declined with longer time from symptom onset to treatment (Table 2). Each 60-minute delay in therapy was associated with a less favourable degree of

disability, cOR 0.80 (95% CI 0.68 to 0.95). Each 60-minute delay was also associated with reduced odds of excellent recovery (mRS 0-1), OR 0.76 (95% CI, 0.58 to 0.99), and a trend toward reduced odds of functional independence (mRS 0-2), OR 0.82 (95% CI, 0.66 to 1.03). In adjusted analysis, the absolute risk difference (ARD) for functional independence between the onset-to-treatment of 0.5-3 hours vs. 3-4.5 hours was 4.5% (32.3% vs 27.8%, Figure 1). Among 42 patients with very fast onset-to-treatment times of 30-60 minutes, the adjusted rate of functional independence at 90 days was 37.5%.

The decline in the rate of good outcomes with longer onset-to-treatment was not modified by age (heterogeneity $p=0.21$), baseline NIHSS score (heterogeneity $p=0.81$), baseline ASPECT score (heterogeneity $p=0.88$), occlusion location (heterogeneity $p=0.67$), diabetes mellitus (heterogeneity $p=0.44$), prior stroke (heterogeneity $p=0.27$), or sex (heterogeneity $p=0.21$) (Figure 2). The absolute decline in the rate of excellent outcome (mRS 0-1 at 90 days) was 8.4 per 1000 patients treated per 15 minutes delay in onset-to-treatment time.

The relation between door to needle time and outcome was stronger than onset to needle time. The odds of excellent recovery (mRS 0-1) and functional independence (mRS 0-2) for each 60-minute delay in door-to-needle was OR (mRS 0-1) 0.51 (95%CI, 0.29 to 0.92) and OR (mRS 0-2) 0.47 (95%CI, 0.28 to 0.80) respectively. The adjusted absolute risk difference for lower functional independence between door-to-needle time intervals of 0-30 vs. 31-60 minutes was 19.3% (45.0% vs 25.7%). The absolute decline in the rate of excellent outcome (mRS 0-1 at 90 days) was 20.3 per 1000 patients treated per 15 minutes delay in door-to-needle time. There was no evidence of an onset-to-treatment time effect on mortality or symptomatic intracranial haemorrhage (Table 2).

DISCUSSION

In this pooled analysis of individual participant-level data of acute ischaemic stroke patients with documented large vessel occlusion receiving alteplase alone, 20% of patients achieved excellent

functional outcome at 90 days. Slower initiation of alteplase therapy was associated with worse outcomes over the entire disability range and lower rates of excellent recovery and functional independence. In contrast, death and symptomatic intracranial haemorrhage did not show onset to treatment time dependency. The rate of decline of benefit with time from symptom onset was modest, though clinically relevant at the systems level; among LVO patients, every 15-minute delay in alteplase start is associated with 8 fewer among 1000 patients achieving excellent (mRS 0-1) outcome at 90 days. In contrast, the rate of decline of benefit with time from hospital arrival (door-to-needle time) was more dramatic among LVO patients, every 15-minute delay in alteplase start is associated with 20 fewer among 1000 patients achieving excellent (mRS 0-1) outcome at 90 days.

These findings are consonant with prior studies demonstrating that alteplase treatment is of benefit for a broad range of patients with acute ischaemic stroke treated within 3 hours,¹⁶ and within 3 to 4.5 hours from the last seen well time.¹⁷ Treatment outcomes in general clinical practice accord with those in the pivotal RCTs, in diverse geographic regions and healthcare systems.¹⁸⁻²⁰ Among this broad patient group, both pooled clinical trials and large clinical practice registries also demonstrated a large time-dependency of benefit from treatment with intravenous alteplase, with treatment sooner after onset associated with improved outcomes.^{2, 21, 22} Disability outcomes at 3 months after treatment with intravenous alteplase alone were less favourable among the LVO patients in the current investigation than among broader cohorts previously investigated. The overall rate of functional independence at 90 days among LVO patients of 34% in the current study is much less than the 44% seen among a broader cohort in the pooled pivotal intravenous alteplase trials.²³ This less favourable outcome rate is consistent with the greater presenting deficit severity and the reduced early reperfusion response of LVO compared to non-LVO patients.

The pace of loss of benefit from stroke onset to alteplase therapy specifically in LVO patients, observed in the current study, appears slightly faster than that for the broader group of all alteplase-eligible patients. Direct comparison with prior studies is not possible because the time-benefit curve analysis of pooled patients from all alteplase trials reported changes with onset-to-treatment in the odds ratio for better outcomes with alteplase versus control, but not the speed of decline in good outcomes within the alteplase-treated group.² The time-benefit curve analysis of patients treated in practice in the US national Get with the Guidelines – Stroke registry reported changes with onset-to-treatment in rates of good outcome at discharge, rather than at 90 days but the results are similar.²¹ In the current study, a fifteen-minute delay in start of alteplase was associated with 8 fewer of 1000 LVO patients achieving excellent (mRS 0-1) outcome at 90 days; in the US national registry study, a fifteen-minute delay in start of alteplase was associated with 7 fewer of 1000 mixed LVO and non-LVO patients achieving excellent (mRS 0-1) outcome at hospital discharge.

A critical observation from the current study is the documentation of the very large absolute magnitude of benefit with fast door-to-needle times, with an estimated number-needed-treat of 5 to achieve one additional independent outcome with treatment less than 30 minutes from hospital arrival compared to greater than 30 minutes. This result implies an imperative to set standards for in hospital processes much more aggressively than currently. While ultimately the onset-to-reperfusion times will physiologically govern the chance of good outcome, the patients in the HERMES analysis were largely selected by imaging characteristics such that patients with very large infarcts (on non-contrast CT, MR or predicted by CTP) or poor pial collateral filling were excluded. This meant that the onset-to-imaging time was less important than the imaging-to-treatment times in predicting outcomes. In addition, there is substantive inaccuracy of documented last known well times, dependent on the recall of patients with acute brain insults or on symptom recognition by proxy observer, introducing noise into onset-to-treatment intervals absent from door-to-needle intervals. These physiological, measurement and trial design factors likely

contribute to the large magnitude of effect size difference between door-to-needle time and onset-to-treatment times.

The decline in benefit due to delays from onset-to-treatment with alteplase therapy alone in LVO patients in the current study is 2.5-fold less (8 vs 20 fewer per thousand independent outcomes per 15 minute delay) than that for endovascular thrombectomy in LVO patients in a prior US national Get with the Guidelines – Stroke study.²⁴ This is consistent with the larger overall treatment benefit magnitude associated with endovascular therapy. However, patient selection by imaging may also play a role in the shallow onset-to-treatment time decay curves for intravenous alteplase treatment patients, by excluding patients with fast progression of ischemia. Although the Get-with-the-Guidelines data are voluntarily collected and reported compared to the more rigorous prospective clinical trial data presented here, these contrasting time-benefit relationships are important inputs into models seeking to optimise ambulance routing strategies for patients with suspected LVO, since direct routing to comprehensive stroke centres will cause longer onset to treatment for alteplase but shorter onset to puncture for thrombectomy.^{25, 26}

Biologically, our results may be partly explained because the probability of early reperfusion with intravenous alteplase only is less than half that with EVT. In the ESCAPE trial,¹⁰ recanalization was measured in the control arm at 2-8 hours after randomization using CT angiography. Despite differences in sub-populations, the rate of early recanalization was 7% in those who were not eligible for and did not receive alteplase, 37% in those who received alteplase alone and 75% in those who received EVT (determined by formal selective cerebral angiography).¹⁰ Key baseline patient factors, including stroke severity and the extent of early ischemic changes, did not alter the time relationship with treatment. Although the European regulation labelling for alteplase in the 3-to-4.5-hour time window, using ECASS-3 data,¹⁷ initially suggested that patients over age 80, with diabetes mellitus or very severe stroke should

not be offered treatment with alteplase, our analyses provide collateral prospective observational evidence that fast treatment is the more important issue.

This study has limitations. Entry criteria differed in some ways across the 7 contributing trials, most notably with 3 of the trials requiring or encouraging the use of more advanced imaging of penumbra or collaterals. However, among patients with LVO, almost all patients have adequate penumbra or collaterals within the first 4.5 hours from onset. Only one trial collected data on early reperfusion subsequent to alteplase use, precluding detailed analysis. We made a simplifying assumption that all patients treated at the endovascular hospital had CTA prior to or immediately after commencing alteplase therapy; however, it remains possible that this was not the case in a small number of patients. The nature of some of the trial protocols resulted in an enriched cohort who did not reperfuse with intravenous alteplase (“non-responders”) which may have resulted in an underestimate of the rate of excellent neurological outcome. Finally, even after pooling across trials, sample size was moderate, limiting precision of time-benefit relation estimates.

In conclusion, disability outcomes at 3 months with alteplase alone are less favourable with slower onset to treatment times. Faster treatment, in particular door-to-needle times less than 30 minutes, are strongly associated with better outcomes.

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Table 1

Baseline characteristics of the alteplase cohort according to onset to treatment times.

Metric	All (n 601)	OTT 0-90 min (n 158)	OTT 91-180 min (n 336)	OTT 181-270 min (n 99)	p-value
Age (years)	66.0 ± 13.9 (601) [68.0] (18.0,96.7)	66.7 ± 12.8 (158) [68.0] (34.0,96.7)	65.4 ± 13.8 (336) [68.0] (18.0,90.0)	66.3 ± 15.5 (99) [69.0] (20.4,90.0)	0.673
Age 80+	12.0% (72/601)	12.7% (20/158)	10.4% (35/336)	13.1% (13/99)	0.652
Female sex	50.1% (301/601)	46.2% (73/158)	52.7% (177/336)	46.5% (46/99)	0.306
Medical History					
Atrial fibrillation	31.0% (112/361)	27.0% (38/141)	32.3% (52/161)	37.7% (20/53)	0.312
Hypertension	59.6% (357/599)	54.1% (85/157)	57.4% (193/336)	75.8% (75/99)	0.001
Hyperlipidemia	42.1% (245/582)	30.8% (48/156)	46.6% (152/326)	45.2% (42/93)	0.003
Diabetes mellitus	18.1% (108/598)	16.6% (26/157)	18.2% (61/336)	19.4% (19/98)	0.838
Prior stroke/TIA	9.4% (56/598)	7.0% (11/158)	9.3% (31/334)	14.1% (14/99)	0.158
Tobacco use	37.0% (204/551)	35.6% (52/146)	39.4% (123/312)	32.2% (28/87)	0.416
Glucose (mg/ dl) (mean, sd (n), median, range)	86.3 ± 87.0 (561) [102.6] (0.0,1236.4)	124.1 ± 101.4 (151) [115.0] (0.8,1236.4)	70.6 ± 78.5 (310) [87.6] (0.0,457.0)	74.3 ± 70.4 (93) [101.8] (0.4,315.0)	<0.001
Pre-stroke mRS					0.810
0	82.2% (296/360)	80.9% (114/141)	82.6% (133/161)	86.5% (45/52)	
1	11.9% (43/360)	12.1% (17/141)	11.8% (19/161)	11.5% (6/52)	
2	2.8% (10/360)	3.5% (5/141)	1.9% (3/161)	1.9% (1/52)	
3+	3.1% (11/360)	3.5% (5/141)	3.7% (6/161)	0.0% (0/52)	
NIHSS at baseline	16.8 ± 5.2 (599) [17.0] (4.0,32.0)	17.1 ± 5.7 (158) [17.0] (4.0,32.0)	17.0 ± 4.9 (335) [17.0] (4.0,29.0)	15.9 ± 5.1 (99) [16.0] (4.0,25.0)	0.098
NIHSS at baseline					0.101
0-10	13.0% (78/599)	17.1% (27/158)	9.6% (32/335)	17.2% (17/99)	
11-15	25.9% (155/599)	19.6% (31/158)	28.7% (96/335)	27.3% (27/99)	
16-20	35.6% (213/599)	36.7% (58/158)	36.4% (122/335)	32.3% (32/99)	
21+	25.5% (153/599)	26.6% (42/158)	25.4% (85/335)	23.2% (23/99)	
Occlusion location					0.063
NA	6.8% (41/601)	4.4% (7/158)	7.4% (25/336)	8.1% (8/99)	
ICA	24.0% (144/601)	32.9% (52/158)	19.9% (67/336)	23.2% (23/99)	
M1-MCA	63.2% (380/601)	56.3% (89/158)	65.5% (220/336)	66.7% (66/99)	
M2-MCA	5.8% (35/601)	6.3% (10/158)	6.8% (23/336)	2.0% (2/99)	
Other	0.2% (1/601)	0.0% (0/158)	0.3% (1/336)	0.0% (0/99)	
ASPECTS	7.6 ± 2.1 (594) [8.0] (0.0,10.0)	8.0 ± 1.8 (155) [8.0] (1.0,10.0)	7.2 ± 2.2 (334) [8.0] (0.0,10.0)	7.8 ± 1.9 (98) [8.0] (2.0,10.0)	0.168
ASPECTS					<0.001
9-10	33.8% (201/594)	44.5% (69/155)	25.7% (86/334)	43.9% (43/98)	
7-8	45.1% (268/594)	40.6% (63/155)	50.9% (170/334)	33.7% (33/98)	
5-6	12.5% (74/594)	8.4% (13/155)	13.2% (44/334)	15.3% (15/98)	
0-4	8.6% (51/594)	6.5% (10/155)	10.2% (34/334)	7.1% (7/98)	
Onset to ED (min)	92.4 ± 58.3 (562) [80.0] (0.0,466.0)	40.3 ± 17.0 (148) [40.0] (0.0,86.0)	88.1 ± 31.7 (314) [86.0] (0.0,180.0)	172.3 ± 35.5 (93) [180.0] (63.0,246.0)	<0.001
Onset to alteplase treatment (min)	133.7 ± 60.4 (600) [125.0] (31.0,525.0)	69.7 ± 14.8 (158) [70.0] (31.0,90.0)	133.5 ± 26.2 (336) [133.0] (91.0,180.0)	218.9 ± 25.5 (99) [219.0] (183.0,270.0)	<0.001
ED arrival to alteplase treatment (min)	42.0 ± 24.4 (562) [38.0] (0.0,157.0)	29.3 ± 14.8 (148) [29.0] (0.0,89.0)	46.0 ± 24.1 (314) [43.0] (0.0,125.0)	47.7 ± 30.4 (93) [42.0] (0.0,157.0)	<0.001

OTT = onset-to-alteplase-treatment time (minutes); TIA = transient ischemic attack; mRS = modified Rankin scale; NIHSS = National Institutes of Health Stroke Scale; ICA = internal carotid artery; M1-MCA = M1 segment (stem) of the middle cerebral artery; M2-MCA = M2 segment (branch) of the middle cerebral artery; ASPECTS = Alberta Stroke Program Early CT Score; ED = emergency department;

Table 2

Effect of onset-to-treatment and door-to-needles times on adjusted patient outcomes.

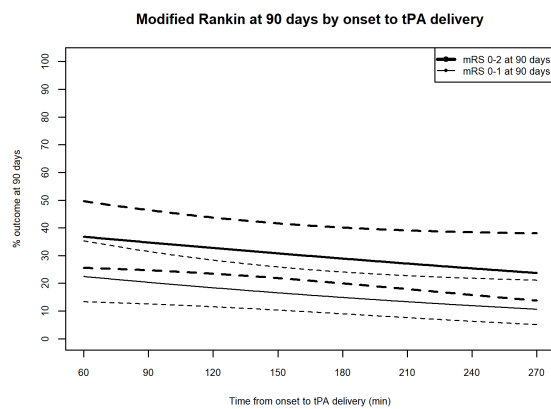
Outcome *	Onset-to-Treatment time (per 60 min)	Door-to-Needle time (per 60 min)
	Odds ratio (95% confidence interval)	Odds ratio (95% confidence interval)
mRS (ordinal)	0.80 (CI ₉₅ 0.68-0.95)	0.55 (CI ₉₅ 0.37-0.81)
mRS 0-2	0.82 (CI ₉₅ 0.66-1.03)	0.47 (CI ₉₅ 0.28-0.80)
mRS 0-1	0.76 (CI ₉₅ 0.58-0.99)	0.51 (CI ₉₅ 0.29-0.92)
Death	0.99 (CI ₉₅ 0.79-1.23)	1.07 (CI ₉₅ 0.59-1.93)
sICH	0.74 (CI ₉₅ 0.43-1.28)	0.44 (CI ₉₅ 0.12-1.66)

mRS = modified Rankin Scale, sICH = symptomatic intracerebral haemorrhage; CI₉₅ = 95% confidence interval

Figure 1

Relationship between onset to treatment time (Figure 1a) and door to treatment time (Figure 1b) with alteplase and the proportion of patients with 90-day functional independence (mRS 0-2 “in black”) and 90-day excellent functional recovery (mRS 0-1 “in red”). Curves are adjusted for age, sex, NIHSS, ASPECTS, occlusion location. Curves have a different breadth along the time axis (abscissa) which attenuates the relative steepness of the slope of ED-arrival-to-tPA-delivery curve. A fifteen-minute delay in start of alteplase from stroke onset was associated with 8 fewer of 1000 LVO patients achieving excellent (mRS 0-1) outcome at 90 days; but the loss of benefit is steeper with a fifteen-minute delay in start of alteplase from ED arrival associated with 20 fewer of 1000 LVO patients achieving excellent (mRS 0-1) outcome at 90 days.

A



B

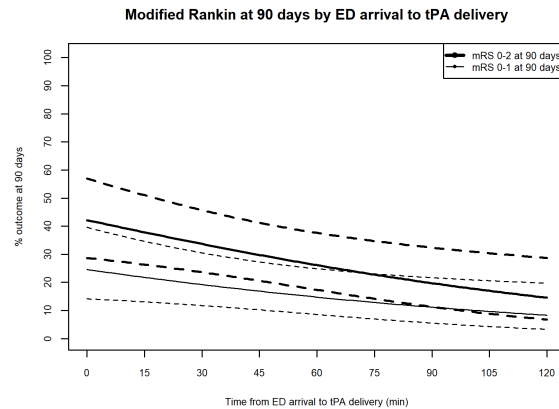
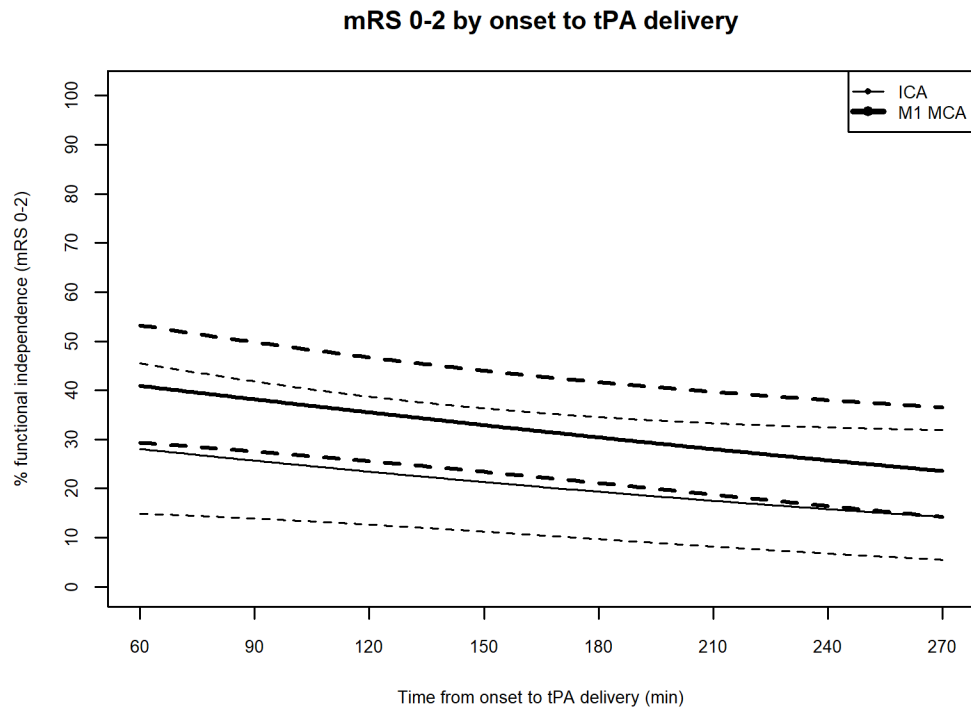


Figure 2:

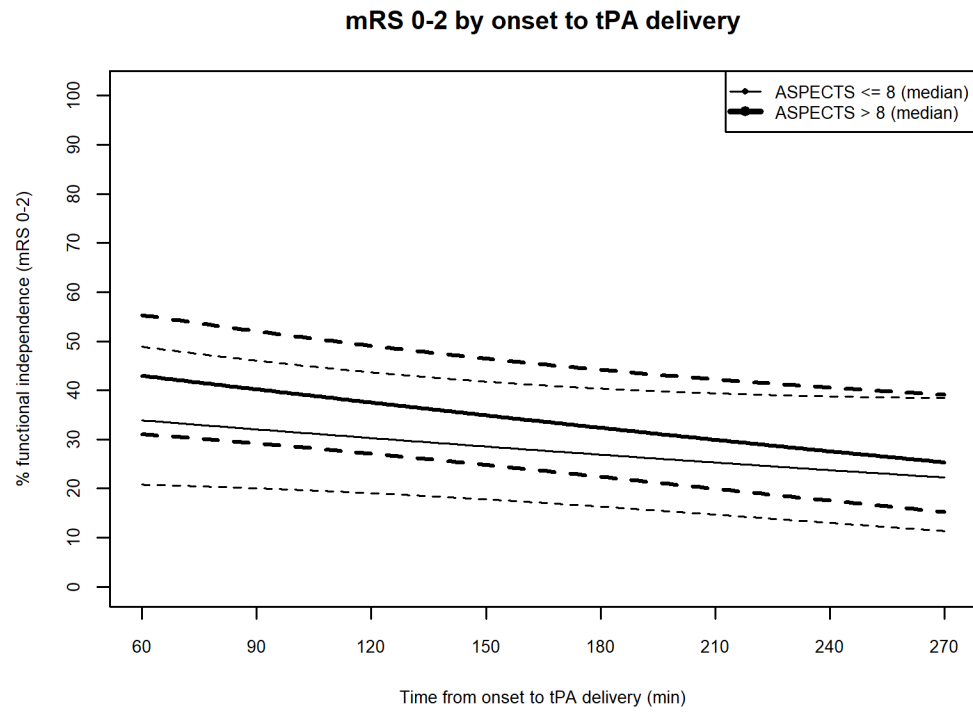
Relation between time from onset to alteplase treatment and functional independence (mRS 0-2) at 3 months in patient subgroups of site of vessel occlusion (A), extent of infarct signs (ASPECT score) (B), age, (C), and presenting stroke deficit severity (NIHSS) (D).

ASPECTS: Alberta Stroke Program Early CT Score, ICA: terminal internal carotid artery, M1: proximal middle cerebral artery “M1”; mRS=modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale

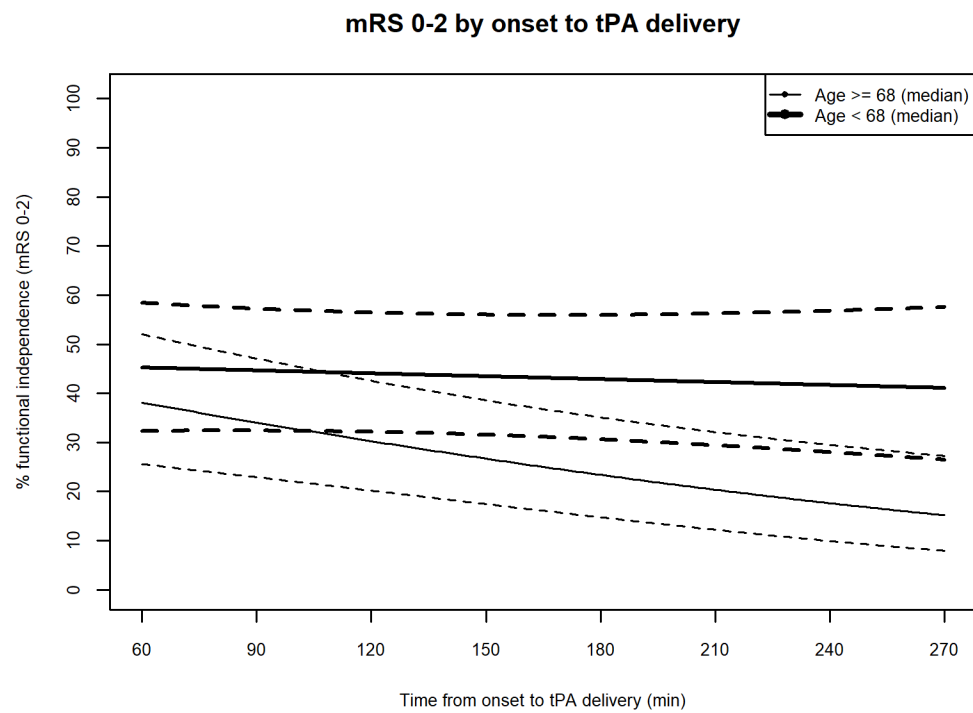
A



B.



C.



D.

